Diagnosis of HIV-related TB: Guidelines, Evidence, Quality Indicators

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Cases from the Field

- A man dies of unrecognized pulmonary KS while being repeatedly treated for tuberculosis
- A child dies of an undiagnosed abdominal malignancy after being diagnosed with extrapulmonary TB on the basis of abdominal ultrasound and treated for > 12 months for TB with no improvement
- A women is diagnosed with extrapulmonary TB based on abnormal liver chemistries with normal chest xray, no cough, no fever, no lymphadenopathy→ she actually had lactic acidosis from stavudine therapy

Outline

- Review South African and WHO guidelines for diagnosis of tuberculosis
- Clinical suspicion for tuberculosis (CSTB)
- Performance characteristics of diagnostic tests
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South African National Guidelines for Diagnosis of Tuberculosis

- TB suspect
- Sputum collection
  - 2 expectorated for microscopy
  - 1 expectorated for C&S (re-treatment cases only)
- Indications for culture
  - Hx previous unsuccessful TB Rx
  - Drug susceptibility necessary
  - Smear + at 2 or 6 months
  - 2 smears negative, no response to antibiotics, clinical suspicion TB
- Indications for CXR
  - When sputum AFB +
    - Suspected complications
    - Haemoptysis
    - Diagnose other lung diseases
    - Only 1 of 2 sputum AFB smears +
  - When sputum AFB –
  - During & end of Rx
    - If response not satisfactory

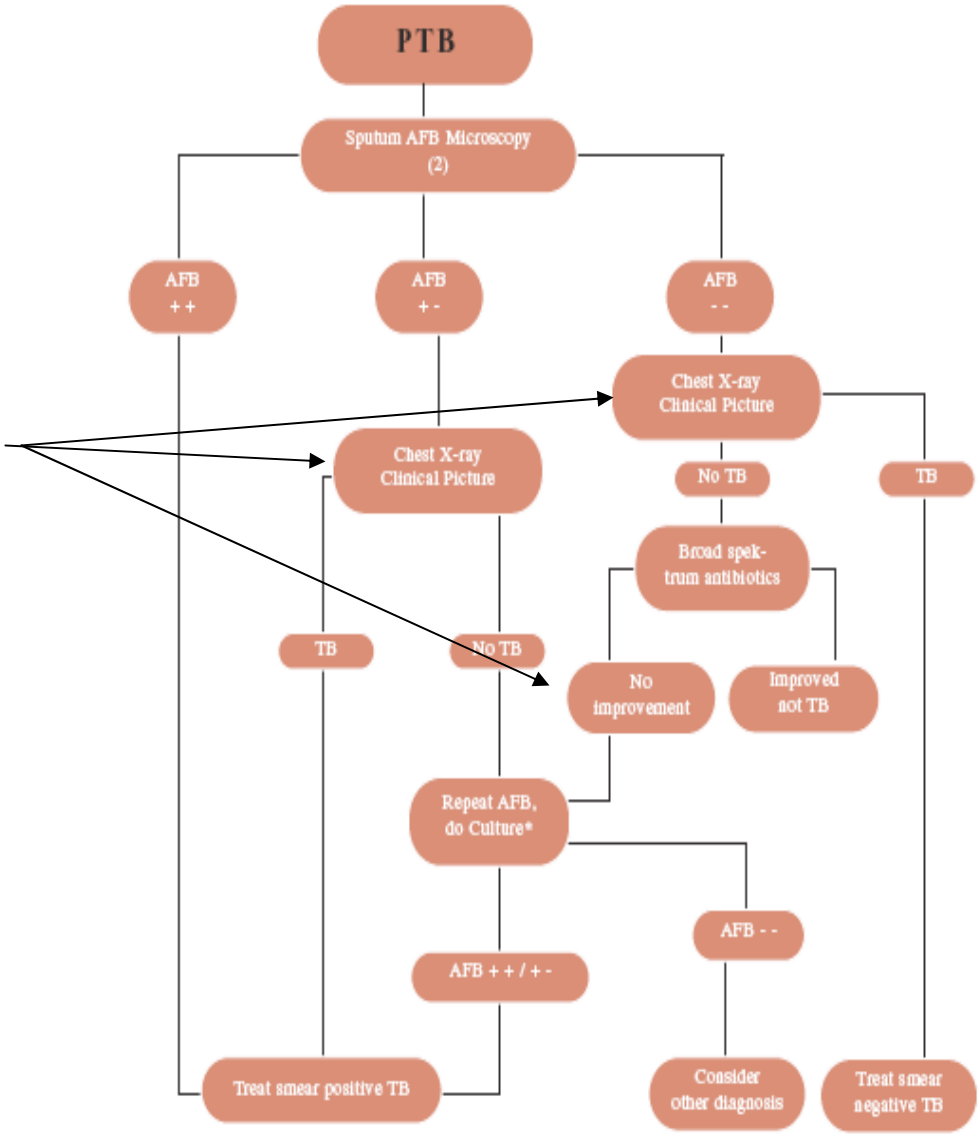
South African National Tuberculosis Control Programme Practical Guidelines 2004

Case Definitions

- Smear + PTB
  - ≥ 2 sputum smears + or
  - 1 smear + and consistent CXR or culture +
  - 1 smear + and clinically ill
- Smear – PTB
  - ≥ 2 smears negative
  - CXR consistent with active TB

4.6 Management plan for pulmonary tuberculosis (PTB)

Clinical Judgment



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Diagnosis of TB in Children

- Clinical Suspicion
  - Long duration exposure
  - High intensity exposure
  - < 2 years old with TB in caregiver
  - Malnutrition
  - HIV + children
  - Failure to thrive
  - Cough > 2 weeks unresponsive to antibiotics
  - Lymphadenopathy unresponsive to antibiotics
  - Fever > 7 days without other cause
- Tuberculin skin test
  - Less likely + if
    - Severe malnutrition
    - HIV infection
    - Disseminated TB
    - Immunosuppressive drugs
  - Prior BCG
    - 10-14 mm
      - TBI or vaccination
    - ≥ 15 mm
      - TB
  - HIV infected
    - ≥ 5 mm
      - TBI

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Chest Radiography in Children

11.7 Chest radiography

Chest radiography is often very useful in making the diagnosis of TB in children. The chest radiographs must however be of good quality and the results depend on the expertise of the person reading them.

The most common radiological signs of childhood TB are:

- An enlarged hilar region of the lung and a broad mediastinum due to enlarged hilar or mediastinal glands. Often compression of the airways due to the enlarged lymph glands can be observed. The enlarged lymph glands can occlude the airway leading to collapse of a lobe.
- The parenchymal lesion can enlarge causing widespread opacification in a segment or lobe of the lung.
- Acute dissemination causes widespread fine millet-sized (1-2 mm) lesions (Miliary TB).
- Pleural effusions that usually occur in children older than six years.

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Table 2: Score chart for diagnosis of TB in children

Feature	0	1	2	3	4	Score
GENERAL						
Weeks of illness	< 2	2 - 4		> 4		
Nutritional status [% weight for age]	> 80%	60-80%		< 60%		
Family history of TB	None	reported by family		proved sputum positive		
Tuberculin test				positive		
Malnutrition				not improving after 4weeks		
Unexplained fever			No response to treatment			
LOCAL						
				Lymph nodes		
				Joint or bone swelling		
				Abdominal mass or ascites		
				CNS signs, Abnormal CSF		
X-rays				Broad mediastinum due to enlarged hilar glands	Angle deformityof spine	
TOTAL						

Table 2 shows a score chart for the diagnosis of childhood TB or screening for TB:
[> : more than; < : less than.]
A score of 7 or more indicates a high likelihood of TB.

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MDR TB

13.1 When to suspect MDR TB

- Retreatment patients who remain sputum smear positive after three months' of intensive Therapy.
- Treatment failure and defaulter cases.
- Close contacts of MDR tuberculosis cases.
- Chronic cases.

13.2 Diagnosing MDR TB

MDR TB is a laboratory diagnosis; it is only diagnosed by TB culture and susceptibility testing.

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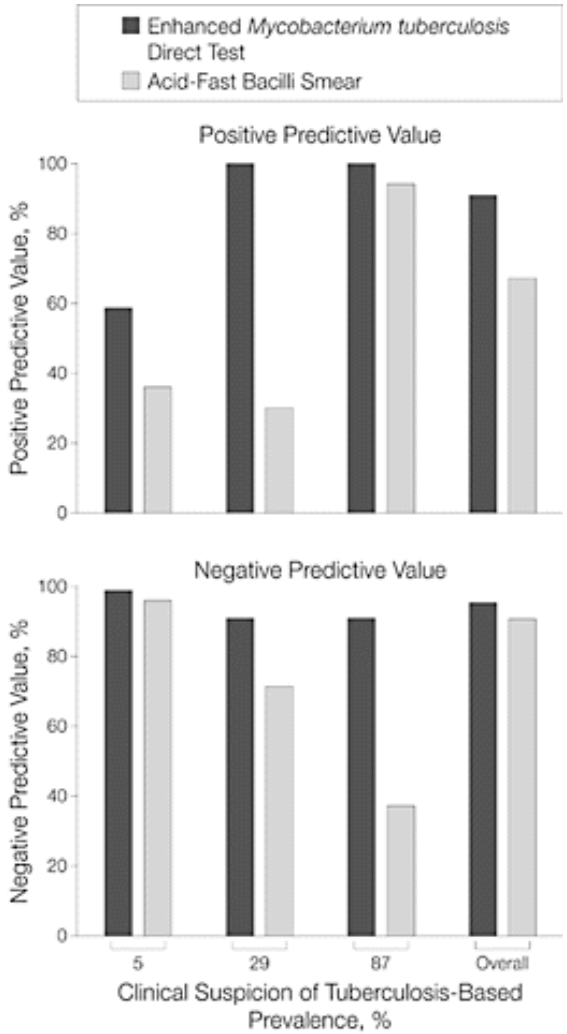
Clinical Suspicion for TB (CSTB)

- The subjective probability of tuberculosis estimated by a clinician
  - after performing a history and physical examination and
  - prior to performing any diagnostic test, e.g.
    - Smear
    - Chest Xray
    - Skin test
    - Culture
    - PCR

Estimated Predictive Value of Acid-Fast Bacilli Smear and Enhanced Mycobacterium tuberculosis Direct Test by Clinical Suspicion for Tuberculosis

Probability TB given + Test

Probability NOT TB given Negative Test



Catanzaro, A. et al. JAMA 2000;283:639-645.

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JAMA

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Performance Characteristics of Diagnostic Tests for TB

- Sensitivity of *expectorated sputum*[1] for PTB
  - 55% (1 sputum)
  - 70% (2 sputa)
  - 70% (3 sputa)
- *Auramine staining* increases yield by 18%[2]

Performance Characteristics of Diagnostic Tests for TB

- *Sputum induction* in patients with negative smears or unable to expectorate has positive yield varying from 13.2%[3] – 29%[4]
- *Sputum concentration* by centrifugation and NaOCl liquefaction increases sensitivity from 54.2% - 67.5% (conventional direct microscopy) to 63.1%[5] -87.1% (concentrated)[6]

Scanty Positive Smear

Scanty smear defined as < 10 AFB per HPF

Table Smear results of patients with scanty AFB grades by culture

Culture	*n* (%)	Smear result combinations: Scanty Negative Negative *n* (%)	Scanty Scanty Negative *n* (%)	Scanty Scanty Scanty *n* (%)	Scanty Positive Negative *n* (%)	Scanty Positive Positive *n* (%)	Scanty Scanty Positive *n* (%)
<3 AFB in all scanty smears							
Positive	15 (79)	6 (60)	5 (100)	0	3 (100)	0	1 (100)
Negative	4 (21)	4 (40)	0	0	0	0	0
One or more scanty smears with ⩾3 AFB							
Positive	48 (94)	6 (75)	8 (89)	9 (100)	3 (100)	0	22 (100)
Negative	3 (6)	2 (25)	1 (11)	0	0	0	0

AFB = acid-fast bacilli.

79% of patients with < 3 AFB in all scanty smears were culture +
94% of patients with one or more scanty smears with ≥ 3 AFB were culture +
Twelve of 18 patients with a single scanty smear and
51 of 52 with 2 scanty smears were culture-positive

Lawson et al. Int J Tuberc Lung Dis 2005;9:933-935

Performance Characteristics of Diagnostic Tests for TB: Chest Radiography

- 4% (10/250) asymptomatic HIV infected patients with normal chest xrays and negative sputum smears were culture + for TB[1]
- Prior to preventive therapy
  - Yield very low unless symptomatic[2,3]
  - But has not been evaluated in setting immediately prior to HAART initiation

Screening for TB prior to IPT

Table Performance of screening tests for tuberculosis in 129 patients with advanced HIV disease

Screening test	Sensitivity %	Specificity %	Odds ratio (95% CI)*	P†
Observed weight loss ⩾2.5% in 4 weeks	81.8	78.8	12.6 (2.9–55.3)	<0.01
Cough >2 weeks	81.8	88.1	20.7 (4.8–89.7)	<0.01
Night sweats >2 weeks	72.7	88.1	12.9 (3.7–45.1)	<0.01
Fever >2 weeks	72.7	83.1	9.6 (2.7–33.9)	<0.01
Mantoux (⩾5 mm induration)	54.5	83.1	4.8 (1.6–14.4)	0.01
Chest X-ray suggestive	27.3	95.8	5.7 (1.9–17.3)	0.02
Sputum smear	54.5	100	N/A	N/A
Sputum culture	90.9	100	N/A	N/A

* Odds ratios adjusted after logistic regression.
† Fisher's exact 2-tailed test.
HIV = human immunodeficiency virus; CI = confidence interval; N/A = not applicable.

Mohammed et al. Int J Tuberc Lung Dis 2004;8:792-795

Role of Chest X-ray for Diagnosis of TB

Table 3: CXR performance on all suspects and on suspects excluding those who were ZN-positive. Culture (patient based) used as gold standard (95% confidence interval)

Score of the reader	Sensitivity	Specificity	PPV	NPV
CXR on all suspects (n = 998)				
a) Highly consistent for TB	68 (64–72)	90 (87–93)	0.90 (0.87–0.93)	0.69 (0.65–0.72)
b) Consistent for TB	23 (19–26)	77 (73–80)	0.55 (0.49–0.62)	0.44 (0.40–0.47)
c) Pathology, but no TB	2 (0–3)	96 (94–98)	0.33 (0.16–0.51)	0.43 (0.40–0.46)
"TB" (a+b)	91 (88–93)	67 (62–71)	0.78 (0.74–0.81)	0.84 (0.81–.088)
"any pathology" (a+b+c)	92 (90–94)	63 (58–67)	0.76 (0.73–0.79)	0.86 (0.82–0.90)
CXR on suspects excluding those who were ZN positive (n = 657)				
a) Highly consistent for TB	48 (42–55)	90 (87–93)	0.72 (0.65–0.79)	0.77 (0.73–0.81)
b) Consistent for TB	31 (25–37)	77 (73–81)	0.42 (0.34–0.49)	0.68 (0.83–0.90)
c) Pathology but no TB	3 (1–5)	96 (95–98)	0.27 (0.9–0.46)	0.65 (0.62–0.69)
"TB" (a+b)	80 (74–85)	67 (62–71)	0.56 (0.50–0.61)	0.86 (0.83–0.90)
The entire diagnostic process (n = 998)				
ZN followed by CXR	93 (91–95)	62 (57–67)	0.76 (0.72–0.79)	0.87 (0.83–0.91)
CXR followed by ZN	89 (86–91)	97(84–90)	0.90 (0.87–0.92)	0.86 (0.83–0.89)

4-category CXR scoring system used to evaluate 2 TB screening strategies.

Van Cleeff et al. BMC Infectious Diseases 2005;
available at http://www.biomedcentral.com/1471-2334/5/111

Antibiotic Trial to Rule Out TB?

Table 3 Sensitivity, specificity and positive and negative predictive values of response to amoxycillin and erythromycin, compared with culture-positive tuberculosis

Drug response to therapy	Culture	
	Positive	Negative
Amoxycillin		
No (TB)	45	29
Yes (no TB)	9	37
Sensitivity 83%; specificity 56%; PPV 61%; NPV 80%		
Erythromycin		
No (TB)	29	11
Yes (no TB)	15	19
Sensitivity 66%; specificity 63%; PPV 73%; NPV 56%		
Amoxycillin and erythromycin		
No (TB)	29	11
Yes (no TB)	24	56
Sensitivity 55%; specificity 84%; PPV 73% NPV 70%		

PPV = positive predictive value; NPV = negative predictive value.

OR 6.15
LR+ 3.4
LR- 0.6

30% responders to antibiotics did have TB & 27% non-responders did not have TB

Wilkinson et al. Int J Tuberc Lung Dis 2000;4:513-518

Antibiotic Trial to Rule Out TB?

Table 4 Sensitivity, specificity and positive and negative predictive values of sputum smear microscopy plus objective response to antibiotic therapy for culture-positive tuberculosis

Microscopy plus response to antibiotics	Culture	
	Positive	Negative
No (TB)	189	11
Yes (no TB)	24	56
Sensitivity 89%; specificity 84%; PPV 95%; NPV 70%		

OR=40
LR+ 5.6
LR- 0.13

Overall performance unaffected by demographic or clinical features, including HIV status.
PPV = positive predictive value; NPV = negative predictive value.

30% who responded to antibiotics and had negative smears were culture + for TB

Wilkinson et al. Int J Tuberc Lung Dis 2000;4:513-518

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Clinical Presentation of TB in HIV Infection

Features of PTB	Stage of HIV Infection	
	Early	Late
Clinical Picture	Often resembles post-primary TB	Often resembles primary TB
Sputum smear results	Often positive	Often negative
Chest X-ray	Often cavities	Often infiltrates No cavities No abnormalities

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Extra pulmonary TB

- 50-70% of TB cases in HIV infected patients are extra-pulmonary
- Common presentations of extra-pulmonary TB
  - Meningitis
  - Lymphadenitis
  - Miliary
  - Pleural effusion
  - Empyema
  - Pericardial Effusion
  - Peritoneal
  - Skeletal

Expanded Case Definitions of Smear Negative and Extrapulmonary TB

- **Study Objectives**
  - **To assess the diagnostic utility of expanded case definitions for HIV-associated smear-negative pulmonary tuberculosis (PTB) and extra-pulmonary TB (EPTB), and**
  - **to derive objective criteria for response to anti-tuberculosis treatment.**

Wilson et al. IJTLB 2006;10:31-38

Expanded Case Definitions of Smear Negative and Extrapulmonary TB

Table 4 Mycobacterial yield of induced sputum, blood and urine culture by case definition in the 130 participants with confirmed and possible TB

Case definition	*n**	Induced sputum		Urine culture *n* (%)	Blood culture *n* (%)
		Smear *n* (%)	Culture *n* (%)		
Pulmonary infiltrate	74	27 (36)	55 (74)	31 (42)	23 (31)
Peripheral nodes	31	8 (26)	19 (61)	9 (29)	8 (26)
Mediastinal nodes	65	21 (32)	52 (80)	31 (48)	23 (35)
Abdominal nodes	15	4 (27)	13 (87)	6 (40)	7 (47)
Pleural exudate	17	3 (18)	11 (61)	3 (18)	1 (6)
Pericardial effusion	9	1 (11)	4 (44)	3 (33)	2 (22)
Ascitic exudate	6	0	4 (67)	3 (50)	2 (33)
Constitutional	4	2 (50)	4 (100)	3 (75)	3 (75)

*From 105 confirmed (culture-positive [*n* = 103] or histological features [*n* = 2]) and 25 possible (objective RTT) TB cases.
TB = tuberculosis; RTT = response to treatment.

Shows yield of induced sputum according to pulmonary & extra-pulmonary syndromes

Wilson et al. IJTLB 2006;10:31-38

Expanded Case Definitions of Smear Negative and Extrapulmonary TB

Table 5 Final diagnosis by case definition in 147 subjects presenting with TB symptoms and meeting at least one case definition

Case definition	Subjects meeting case definition* *n* (%)	Subjects presenting with this as only case definition *n* (%)	Confirmed TB *n* (%)	Possible TB *n* (%)	Not TB *n* (%)	Positive predictive value of case definition† %
Pulmonary infiltrate	83 (56)	24 (29)	64 (77)	12 (14)	7 (8)	92
Peripheral nodes	33 (23)	11 (33)	30 (91)	1 (3)	2 (6)	94
Mediastinal nodes	69 (47)	7 (10)	59 (86)	7 (10)	3 (4)	96
Abdominal nodes	17 (12)	6 (35)	13 (76)	3 (18)	1 (6)	94
Pleural exudate	20 (14)	3 (15)	14 (70)	3 (15)	3 (15)	85
Pericardial effusion	10 (7)	5 (50)	5 (50)	4 (40)	1 (10)	90
Ascitic exudates	6 (4)	3 (50)	6 (100)	0	0	100
Constitutional	11 (8)	11 (100)	4 (36)	0	7 (64)	36

* Seventy-nine subject (54%) met more than one case definition
† For confirmed (culture positive or histological features) and possible (objective RTT) TB.
TB = tuberculosis, RTT = response to treatment.

More than half of the patients met more than 1 case definition
Predictive values of case definitions were >85% except for “constitutional symptoms”

Wilson et al. IJTLB 2006;10:31-38

“Admitting Defeat”

“While our hats are off to the legions of health workers laboring under such constraints, what matters here is not the success of the proposed clinical algorithm to diagnose TB, but the **failure of the laboratory test, namely microscopy**, meant to perform that function. This retreat to a slow and complex diagnostic approach highlights the desperate status of TB tests currently used in the developing world.”

Perkins & Small. INT J TUBERC LUNG DIS 2006;10(1):1

“Admitting Defeat”

“The drift towards syndromic management of suspected TB occurring in the face of poor diagnostics is fraught with hazards. Lack of diagnostic confirmation results either in missed cases, with consequent morbidity and transmission, or overtreatment of non-TB cases, wasting limited resources and neglecting the true causes of disease. This latter concern is not theoretical. Mortality among patients mistreated as smearnegative TB, especially when HIV-infected, is extremely high.”

Perkins & Small. INT J TUBERC LUNG DIS 2006;10(1):1

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Quality Indicators for TB Diagnosis with HIV Infection

- Distinguish between smear negative cases and no smear submitted cases.
  - Track both
- Monitor proportion of deaths within 4 weeks of starting HRZE as possible indicator of death from other causes
- Clinician performance on case based trainings and evaluations of competence in assigning clinical suspicion of TB (CSTB) and recognition of appropriate differential diagnoses